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THE CHEMISTRY OF THE TETRACYCLIC DITERPENOIDS—IV

THE PARTIAL SYNTHESIS OF(−)-KAUR-16-EN-19-OIC ACID FROM 7-HYDROXYKAURENOLIDE[1]

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Abstract—Hydrogenolysis of 7-oxokaurenolide and Wolff–Kishner reduction of the derived keto-acid gave (−)-kaur-16-en-19-oic acid.

(−)-Kaur-16-en-19-oic acid (V) has been isolated from *Ricinocarpus stylosus*[2] and from the mould *Gibberella fujikuroi* Acc 917.[3] In view of its implication in the biosynthesis of the gibberellins[4] and the kaurenolides, its partial synthesis from 7-hydroxykaurenolide was attempted. The acid, which shows an interesting gibberellin-like biological activity,[5] has recently been totally synthesized.[6] This paper describes in detail a successful partial synthesis which has been briefly reported elsewhere.[7]

7β-Hydroxykaurenolide (I) was oxidized with 8N-chromium trioxide to its 7-ketone (II).[8] Trial experiments indicated that hydrogenolysis of the keto-lactone with zinc and acetic acid led, not unexpectedly, to isomerization of the Δ^{16} double bond. However, reduction with calcium in liquid ammonia followed by oxidation and methylation with diazomethane, led to the keto-ester (III). Alternatively, reduction of the keto-lactone with sodium borohydride led to attack from the less hindered β face of the molecule to give the 7α-hydroxykaurenolide (IV). In this hydroxy-lactone, as opposed to its 7-epimer, there is a *trans* diaxial relationship between the 6α-hydroxyl (blocked as the lactone) and the 7β-hydrogen. Hence on hydrolysis and methylation with sodium methoxide a readily separable mixture of the 7-keto-ester (III) and the diol (VI) was isolated. The former arose through the diaxial elimination of water. Both these methods avoid the facile isomerization of the Δ^{16} exocyclic methylene and permit the removal of the C-6 oxygen by reactions which preclude epimerization at the adjacent ring junction.

Hydrolysis of the keto-ester with 3N-sodium hydroxide gave the corresponding carboxylic acid. Wolff–Kishner reduction of the 7-keto acid led to the required (−)-kaur-16-en-19-oic acid (V) which was identical to the naturally occurring acid.

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[1] Previous part, J. R. Hanson, *Tetrahedron* **22**, 3185 (1966).

[2] C. A. Henrick and P. R. Jefferies, *Chem. and Ind.* 1802 (1963); *Aust. J. Chem.* **17**, 915 (1964).

[3] J. MacMillan, private communication.

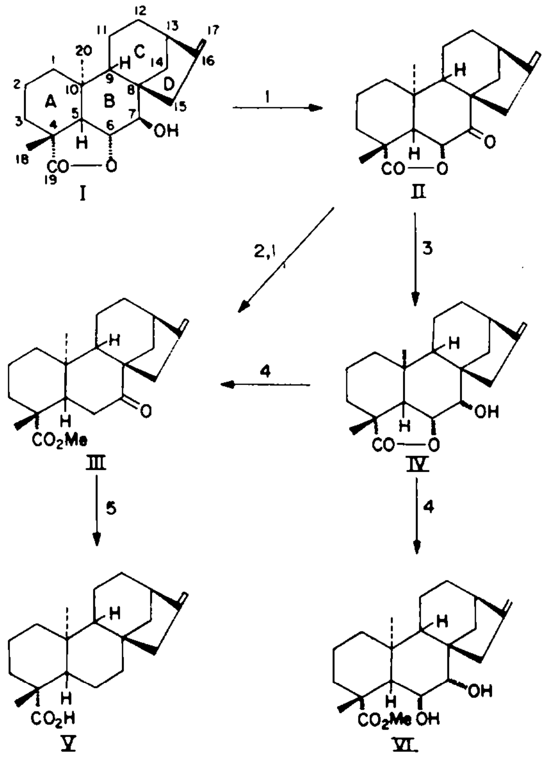
[4] B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 295 (1964); R. H. B. Galt, *J. Chem. Soc.* 3143 (1965).

[5] M. Katsumi, B. O. Phinney, P. R. Jefferies and C. A. Henrick, *Science* **144**, 849 (1964).

[6] K. Mori and M. Matsui, *Tetrahedron Letters* 175 (1966).

[7] R. H. B. Galt and J. R. Hanson, *Chem. and Ind.* 837 (1964).

[8] B. E. Cross, R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.* 2944 (1963).



1, CrO_3; 2, Ca/NH_3; 3, $NaBH_4$; 4, NaOH, CH_2N_2; 5, N_2H_4, KOH

EXPERIMENTAL

General experimental details are as described in Part I.[8]

Hydrogenolysis of 7-oxokaurenolide (II). Ca metal (1 g) was shredded and dissolved in liquid ammonia (300 ml). The ketone[8] (0·65 g) in dioxan (50 ml) was added with stirring. The soln was left until the blue colour returned and then NH_4Cl (5 g) was added and the ammonia evaporated. Water was added and the soln extracted with ether. The extract was washed with dil HCl, water, dried and evaporated to give a gum which was methylated with ethereal diazomethane. This ester was taken up in acetone (5 ml) and oxidized with the 8N CrO_3 reagent (0·3 ml). MeOH was added, the soln concentrated, diluted with water and extracted with ether. The extract was washed with dil HCl, water dried and evaporated to gum which was chromatographed on alumina. Elution with light pet. gave *methyl 7-oxo-(−)-kaur-16-en-19-oate* (III; 0·4 g) which crystallized from light pet. as needles, m.p. 110–112°. (Found: C, 76·3; H, 9·3. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·15%), ν_{max} 1706, 1656, and 871 cm^{-1}.

Hydrolysis of the lactone (IV). The lactone[8] (IV, 130 mg) was refluxed for 4 hr under N_2 in a soln of sodium MeONa (from Na 0·5 g) in MeOH (25 ml). The soln was cooled in ice, cautiously acidified with dil HCl and the organic material recovered in ether and methylated with diazomethane. Chromatography on alumina gave the keto ester (III; 30 mg) and the diol (VI; 60 mg) identified by their IR spectra.

Hydrolysis of the keto-ester (III). The keto-ester (123 mg) in MeOH (1 ml) and 3N NaOH (15 ml) was heated under reflux overnight. The soln was washed with ether and acidified and the organic material recovered in ether. Chromatography on silica gel in 15% AcOEt–light pet. gave *7-oxo-(−)-kaur-16-en-19-oic* acid (85 mg) which crystallized from acetone–light pet. as needles, m.p.

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[8] J. R. Hanson, *Tetrahedron* **22**, 1453 (1966).

208–210°. (Found: C, 75·2; H, 9·0. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%), ν_{max} 3205, 1724, 1689, 1655 and 870 cm^{-1}.

Wolff–Kishner reduction of the above keto acid. The keto acid (72 mg) in diglyme (5 ml) and hydrazine hydrate (0·5 ml) was heated at 150° for 2 hr. KOH pellets (0·6 g) were added and the temp raised to 210° for 1 hr. The soln was poured into water, acidified with dil HCl and extracted with ether. Recovery gave (−)-*kaur-16-en-19-oic acid* (I) (41 mg) which crystallized from acetone–light pet. as needles, m.p. 165–167°, $[\alpha]_D^{17}$ −112° (*c*, 0·25). (Found: C, 79·0; H, 10·1. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%), ν_{max} 2704, 2639, 1691, 1658 and 872 cm^{-1}.

The *methyl ester*, prepared with diazomethane, crystallized from methanol as needles, m.p. 71–73°. (Found: C, 80·2; H, 10·3. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%), ν_{max} 1724, 1655 and and 874 cm^{-1}.

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